REMARKS AND ARGUMENTS

The 35 U.S.C. § 112, First Paragraph Scope of Enablement Rejection

The Examiner has rejected claims 2-7 under 35 U.S.C. § 112, first paragraph, for failure to comply with the enablement requirement. Specifically, the Examiner has stated that the specification does not enable one skilled in the art to which it pertains to make or use the invention commensurate with the scope of the claims.

The first paragraph of Section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A 1971). A specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.* The Wands court set forth a number of non-exclusive factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows:

(1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the relative skill of those in the art,

(7) the predictability or unpredictability of the art, and

(8) the breadth of the claims.

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

The Breadth of the Claims

It is argued in section 3 of the office action that the claims are unduly broad because they encompass an enormous genus of nucleic acid sequences, a portion of which are ligands for TGFβ2. Applicant first notes that the claims all recite the presence of a TGFβ2 nucleic acid ligand. A "nucleic acid ligand" is defined at page 9, lines 19-20, as a non-naturally occurring nucleic acid having a desirable action on a target. In this case, the target is TGFβ2. In other words, the claims encompass only complexes of nucleic acids that are nucleic acid ligands of TGFβ2. The assertion in section 3 of the office action that only a portion of the nucleic acids encompassed by the claims are TGFβ2 ligands--which implies that the remaining portion are not TGFβ2 ligands--is therefore inaccurate.

The specification provides numerous TGFβ2 nucleic acid ligands (SEQ. ID. NO:1-216). Furthermore, the specification teaches in great detail methods for the identification of further nucleic acid ligands of TGFβ2. See, for example, Example 1 (providing several detailed molecular biology protocols for the identification of TGFβ2 nucleic acid ligands).

It is also argued in section 3 of the office action that the claims encompass an enormous genus of non-immunogenic high molecular weight compounds, including such compounds as a test tube or microscope slide. Applicants respectfully note that during patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). The term "non-immunogenic high molecular weight compound" is defined at page 13, lines 3-7 of the specification as a compound between approximately 100 Da

to 1,000,000 Da, more preferably approximately 1000 Da to 500,000 Da, and most preferably approximately 1000 Da to 200,000 Da, that typically does not generate an immunogenic response. One skilled in the art would not consider an object such as a slide or a test tube to be a "compound" in this sense, nor would one skilled in the art refer to such objects as having a "molecular weight."

A Dalton ("Da") is known in the art to be 1.657×10^{-24} grams. Therefore, a compound of 1,000,000 Da would weigh 1.657×10^{-18} grams. This is clearly many orders of magnitude less than the weight of the exemplified objects. One skilled in the art would fully understand the scope of the term "non-immunogenic high molecular weight compound" in light of this definition, which provides both the properties and sizes of the contemplated compounds. Furthermore, examples of such compounds are provided in the specification (see page 13 lines 8-13).

The specification also teaches methods for attaching a non-immunogenic high molecular weight compound or a lipophilic compound to a TGFβ2 nucleic acid ligand (see, for example, page 13, lines 23-page 14, line 5). Additional non-immunogenic high molecular weight compounds and lipophilic compounds, and additional methods for the attachment of those compounds to nucleic acids are known to those skilled in the art. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)

In summary, the specification teaches one skilled in the art how to identify nucleic acid ligands to TGFβ2. The specification also teaches exemplary non-immunogenic high molecular weight compounds and lipophilic compounds, and further teaches methods for complexing those compounds with the identified TGFβ2 nucleic acid ligands; further compounds and complexation methods are known to those skilled in the art. In light of these arguments, it can be seen that the breadth of the claims reasonably correlates with the scope of enablement.

Nature of the Invention

It is argued that the nature of the invention is such that nucleic acid ligands are selected using varying degrees of specificity between ligands and targets. It is further argued that the specification teaches that the selection and amplification is continued until a selected goal is achieved, but that the specification does not teach or describe the metes and bounds of those goals or obtained ligands so as to enable one of skill in the art to make or use the claimed invention.

It is respectfully submitted that the metes and bounds of those goals or obtained ligands are expressly described throughout the specification. At page 12, lines 1-6, the specification states:

> By repeating the partitioning and amplifying steps above, the newly formed candidate mixture contains fewer and fewer weakly binding sequences, and the average degree of affinity of the nucleic acids to the target will generally increase. Taken to its extreme, the SELEX process will yield a candidate mixture containing one or a small number of unique nucleic acids representing those nucleic acids from the original candidate mixture having the highest affinity to the target molecule.

At page 16, lines 8-13, the specification states:

> In order to produce nucleic acids desirable for use as a pharmaceutical, it is preferred that the nucleic acid ligand: 1) binds to the target in a manner capable of achieving the desired effect on the target; 2) be as small as possible to obtain the desired effect; 3) be as stable as possible; and 4) be a specific ligand to the chosen target. In most situations, it is preferred that the nucleic acid ligand have the highest possible affinity to the target.

Thus, the specification expressly teaches that the main selected goal is the provision of TGFβ2 nucleic acid ligands having the highest affinity achievable in the SELEX process. Further goals include the provision of TGFβ2 nucleic acids ligands having high specificity, small size, and great stability. Thus, the specification does teach and describe the metes and bounds of the goals or obtained ligands so as to enable one of skill in the art to make or use the claimed invention.

Level of Predictability in the Art

It is argued that given the similarities between members of the TGFβ family, the level of predictability with respect to TGFβ2-specific ligands is very low. Applicants assume that this argument is made with reference to the specificity of TGFβ2 nucleic acid ligands *i.e.* that TGFβ2 nucleic acid ligands may bind to other TGFβ species.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. *MPEP* § 2164.03.

Applicants note that at page 39, line 1-page 40, line 8, the specification teaches and exemplifies methods for routinely and rapidly evaluating the specificity of TGFβ2 ligands. The results indicate that the chosen TGFβ2 nucleic acid ligands inhibit TGFβ2 bioactivity, but not TGFβ1 bioactivity or TGFβ3 bioactivity. In nucleic acid binding assays, the TGFβ2 nucleic acid ligand does not bind significantly to TGFβ3.

The specification also teaches that the level of predictability is relatively high. Specifically, at page 40, lines 9-18, the specification teaches that TGFβ2 has 19 amino acids that are not found in TGFβ1 or TGFβ3, and also teaches that three of those differences are within a putative heparin binding region which may be important for determining the specificity of TGFβ ligands.

In addition, one skilled in the art is aware that the specificity of *any* type of ligand--including monoclonal antibodies--should be tested if that ligand is generated against a member of a family of related proteins.

Furthermore, with specific reference to nucleic acid ligands, one skilled in the art would be aware that methods exist that can be used during the SELEX process to selectively remove

nucleic acid ligands that bind to a related protein. This method is termed the Counter-SELEX method, and is specifically referred to on page 4, lines 8-13.

Thus, the specification provides ample guidance regarding techniques for evaluating the specificity of TGFβ2 nucleic acid ligands. The specification also refers to well-known, prior art methods that can be used to identify highly specific nucleic acid ligands able to discriminate between closely related molecules. These methods may be rapidly and routinely performed and do not constitute undue experimentation for one skilled in the art. Moreover, the degree of predictability is relatively high given the amino acid differences between TGFβ3 and the related TGFβ1 and TGFβ2 proteins. For these reasons, it is respectfully submitted that the claims are fully enabled by the disclosure.

Existence of Working Examples

It is argued that the specification does not provide working examples of the claimed invention that would enable one of ordinary skill in the art to make and use the invention as claimed.

For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of the level of skill, the state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. *MPEP* § 2164.02. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

The instant application teaches specific TGFβ2 ligands, and also provides extensive protocols for the identification of further TGFβ2 ligands. The application also provides methods for the attachment of TGFβ2 ligands to non-immunogenic high molecular weight compounds or lipophilic compounds. The modification of nucleic acids with lipophilic compounds and non-immunogenic high molecular weight compounds is a mature art, as evidenced on page 12, lines 13-29 where numerous patents and patent applications describing such modifications are described. Given such teachings, it is not necessary for the application to provide *any* working

examples in order to allow one to make and use the claimed genus without undue experimentation.

Undue Experimentation

The examiner's analysis must consider all the evidence related to *each* of the *Wands* factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands* 858 F.2d at 737, 740, 8 USPQ2d at 1404, 1407.

It is noted that the state of the prior art and the level of one of ordinary skill in the art have not been considered in the office action. With regard to the state of the prior art, it is noted that the field of SELEX-derived nucleic acid ligands is a very mature art. This is evidenced by the fact that at the time the application was filed, there were over 70 issued patents in the United States alone with the phrase "nucleic acid ligand" or "SELEX" in their abstracts (using the USPTO's Full-Text database). This includes patents directed to complexes of nucleic acid ligands with non-immunogenic high molecular weight compounds or lipophilic compounds (see page 12, lines 13-29 of the instant specification). Furthermore, the level of one of ordinary skill in the art is very high, Ph.d. level or higher. These factors alone weigh heavily in favor of the conclusion that the claims are enabled.

The instant application teaches specific TGFβ2 ligands, and also provides extensive protocols for the identification of further TGFβ2 ligands having desired specificities and affinities. The application also provides extensive guidance regarding rapid and routine techniques for evaluating the specificity of TGFβ2 nucleic acid ligands. The degree of predictability of the specificity of TGFβ2 ligands is relatively high given the amino acid differences between TGFβ3 and the related TGFβ1 and TGFβ2 proteins. The application also provides methods for attaching a non-immunogenic high molecular weight compound or a lipophilic compound to a TGFβ2 nucleic acid ligand; numerous examples of these compounds are provided in the application, and even further examples would be apparent to one skilled in the art. A working example of the invention is provided. The field of nucleic acid ligands in general, and the sub-field of complexes of nucleic acid ligands, were both mature at the time the application was filed, and the level of one of ordinary skill in the art was very high. In light of

all of these factors, it would not require undue experimentation for one skilled in the art to practice the claimed invention. Withdrawal of the rejection of claims 2-7 for lack of enablement under 35 U.S.C. § 112, first paragraph is respectfully requested.

The 35 U.S.C. § 112, First Paragraph Written Description Rejection

Claims 2-7 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Guidelines for Examination of Patent Applications under the 35 USC 112, 1, "Written Description" Requirement, MPEP § 2163 II.A.3(a) (hereinafter, "Written Description Guidelines") state

> Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient [citing Eli Lilly, 43 USPQ2d at 1406]. Patents and printed publications in the art should be relied upon to determine whether an art is mature and what the level of knowledge and skill is in the art. In most technologies which are mature, and wherein the knowledge and level of skill in the art is high, a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and function of the invention [citation omitted]. [emphasis added]

The level of skill and knowledge in the relevant art, as reflected by patents and printed publications, indicate that the art is mature. This is evidenced by the fact that at the time the application was filed, there were over 70 issued patents in the United States alone with the

phrase "nucleic acid ligand" or "SELEX" in their abstracts (using the USPTO's Full-Text database). This includes patents directed to complexes of nucleic acid ligands with non-immunogenic high molecular weight compounds or lipophilic compounds (see page 12, lines 13-29 of the instant specification). Thus, this is a mature technology where the level of skill is high and advanced. In technologies which are mature, and where the knowledge and level of skill in the art is high, the Written Description Guidelines provide (see above) that a written description question should not be raised for original claims even if the specification discloses only a method of making the invention and the function of the invention. In the present case, therefore, even if the specification disclosed only the SELEX method and methods for complexing nucleic acid ligands with non-immunogenic, high molecular compounds or lipophilic compounds, a written description rejection should not be made. The present specification discloses even more than a method and function, however. The present invention discloses 216 nucleic acid ligands to TGFβ2, and further discloses a specific complex of a TGFβ2 ligand and a polyethylene glycol.

According to the Written Description Guidelines, *MPEP* § 2163 II.A.3(a), the "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." Applicants are in possession of the genus of complexes of TGFβ2 nucleic acid ligands because the SELEX method was well known and advanced, because non-immunogenic high molecular weight compounds and lipohilic compounds were well known, and because methods for attaching such compounds to nucleic acids were well known.

For the foregoing reasons, Applicants respectfully submit that the specification meets the written description requirement of Section 112, and request that the rejection be withdrawn.

The 35 U.S.C. § 102 Rejection

Claims 2-7 stand rejected as being anticipated under 35 U.S.C. § 102(e) by Gold et al., U.S. Patent No. 6,124,449. Applicants hereby submit declarations under 37 C.F.R. § 1.132 showing that the invention disclosed but not claimed in Gold et al. was derived from co-inventors Gold and Pagratis of the instant application. The declarations are submitted unsigned;

signed versions will be submitted by way of a supplemental amendment and response when available. Withdrawal of the 35 U.S.C. § 102(e) rejection is respectfully requested.

The Double Patenting Rejections

U.S. Patent No. 6,713,616 and U.S. Patent No. 6,346,611

Claims 2-7 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-14 of U.S. Patent No. 6,713,616, and over claims 1-5 of U.S. Patent No. 6,346,611. While not acquiescing in these rejections, Applicants hereby submit a terminal disclaimer. It is believed that that the terminal disclaimer is sufficient to overcome the double-patenting rejection.

U.S. Patent No. 6,124,449

Claims 2-7 also stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,124,449. It is argued that the claims of both the '449 patent and the instant application are drawn to TGFβ2, and that column 10, lines 25-44 of the '449 patent teaches the preferred form of ligands is complexed to a non-immunogenic high molecular weight compound.

The Applicants first note that claim 1 of the '449 patent is drawn to purified and isolated non-naturally occurring TGFβ1 nucleic acid ligands, not to TGFβ2 nucleic acid ligands as is argued in section 10 of the office action. Moreover, Applicants note that in an obviousness-type double patenting rejection it is not appropriate to consider the disclosure of the cited patent in determining the obviousness of the invention claimed in the pending application. See *MPEP 804 II.B.1* ("When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art."). Therefore, the teachings at column 10, lines 25-44 of the '449 patent are not available for the purposes of establishing an obviousness-type double patenting rejection.

Applicant respectfully traverses the obviousness-type double patenting rejection. The examiner bears the burden of establishing a *prima facie* case of obviousness. Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. Because the teachings of the '449 patent relied on by the Examiner are not available as a prior art reference, a *prima facie* case of obviousness has not been made. Specifically, the examiner has not established that a claim to an isolated and purified TGFβ1 ligand renders obvious a claim to a ligand to different protein (TGFβ2) in a different form (complexed rather than purified and isolated). At the very most, it would have been obvious to try and make TGFβ2 ligand complexes. "Obvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). Thus, Applicant submits that claims to TGFβ2 ligand complexes are not mere obvious variations of the invention defined in claim 1 of United States Patent No. 6,124,449. Reconsideration is respectfully requested.

U.S. Patent No. 5,731,424 in view of U.S. Patent No. 6,124,449

Claims 2-7 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 5,731,424 in view of U.S. Patent No. 6,124,449.

Applicants first note that that U.S. Patent No. 6,124,449 is not available as a prior art reference with which to evaluate whether the pending claims of the instant application are a mere obvious variation of claims 1-11 of U.S. Patent No. 5,731,424. As discussed above in the section entitled "The 35 USC § 102 Rejection," Applicants have enclosed declarations under 37 C.F.R. § 1.132 showing that the invention disclosed but not claimed in the '449 was derived from co-inventors Gold and Pagratis of the instant application. Therefore, the '449 patent is not a 35 U.S.C. § 102(e) reference and reference to the teachings found at column 10, lines 25-44 of the '449 patent is not appropriate.

Similarly, the *disclosure* of U.S. Patent No. 5,731,424 is not available for the purposes of establishing an obviousness-type double patenting rejection. See *MPEP 804 II.B.1* ("When considering whether the invention defined in a claim of an application is an obvious variation of

the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art.").

Applicant respectfully traverses the obviousness-type double patenting rejection. The examiner bears the burden of establishing a *prima facie* case of obviousness. Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. Because the teachings of U.S. Patent No. 6,124,449 and U.S. Patent No. 5,731,424 relied on by the Examiner are not available, a *prima facie* case of obviousness has not been made. Specifically, the examiner has not provided any showing that claim to TGFβ2 ligand complexes are mere obvious variations of claims drawn to uncomplexed TGFβ and TGFβ1 ligands. At the very most, Applicants submit that it would have been obvious to try and make TGFβ2 ligand complexes. "Obvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). Thus, Applicant submits that claims to TGFβ2 ligand complexes are not mere obvious variations of the invention defined in claim 1-11 of United States Patent No. 5,731,424. Reconsideration is respectfully requested.

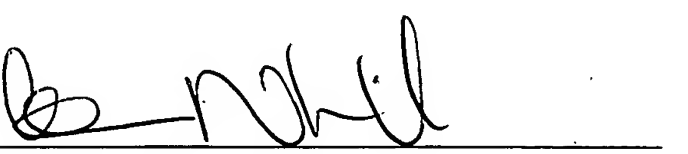
Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

Date: September 20, 2004



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